Amendments to the Specification:

Please replace the paragraph beginning at page 7, line 16 and ending on page 7, line 23 with the following rewritten paragraph:

-- ~~The~~As such, the present invention ~~also provides methods for selectively inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells, as well as methods~~relates to a method of treating cancer ~~and of chemoprevention~~ in ~~subjects~~a subject in need thereof, by administering to ~~said subject an effective amount of a pharmaceutical composition comprising a HDAC inhibitor~~a subject in need thereof a first amount of suberoylanilide hydroxamic acid (SAHA) or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or diluent. An effective amount of an HDAC inhibitor in the present invention can be up to~~ at a total daily dose of up to 800 mg~~.~~ in a first treatment procedure, and a second amount of an anti-cancer agent in a second treatment procedure, wherein the first and second amounts together comprise a therapeutically effective amount. --

Please replace the paragraph beginning at page 9, line 4 and ending on page 9, line 9 with the following rewritten paragraph:

-- In another embodiment, the HDAC inhibitor is a hydroxamic acid derivative selected from the group consisting of m-carboxycinnamic acid bishydroxamide (CBHA), Trichostatin A (TSA), Trichostatin C, ~~Salicylihydroxamic~~ Salicylhydroxamic Acid (SBHA), Azelaic Bishydroxamic Acid (ABHA), Azelaic-1-Hydroxamate-9-Anilide (AAHA), 6-(3-Chlorophenylureido) carpoic Hydroxamic Acid (3Cl-UCHA), Oxamflatin, A-161906, Scriptaid, PXD-101, LAQ-824, CHAP, MW2796, and MW2996. --

Please replace the paragraph beginning at page 19, line 3 and ending on page 19, line 13, with the following rewritten paragraph:

-- For example, an enzymatic assay to determine the activity of ~~a histone deacetylase~~an HDAC inhibitor compound can be conducted as follows. Briefly, the effect of an HDAC inhibitor compound on affinity purified human epitope-tagged (Flag) HDAC1 can be assayed by incubating the enzyme preparation in the absence of substrate on ice for about 20 minutes with the indicated amount of inhibitor compound. Substrate

([^{3}H]acetyl-labelled murine erythroleukemia cell-derived histone) can be added and the sample can be incubated for 20 minutes at 37°C in a total volume of 30 μL. The reaction can then be stopped and released acetate can be extracted and the amount of radioactivity release determined by scintillation counting. An alternative assay useful for determining the activity of ~~a histone deacetylase~~an HDAC inhibitor compound is the "HDAC Fluorescent Activity Assay; Drug Discovery Kit-AK-500" available from BIOMOL® Research Laboratories, Inc., Plymouth Meeting, PA. --

Please replace the section beginning at page 20, line 4 and ending on page 20, line 10, with the following rewritten section:

-- Thus, the present invention includes within its broad scope compositions comprising HDAC inhibitors which are 1) hydroxamic acid derivatives; 2) Short-Chain Fatty Acids (SCFAs); 3) cyclic tetrapeptides; 4) benzamides; 5) electrophilic ketones; and/or any other class of compounds capable of inhibiting histone deacetylases, for use in inhibiting histone deacetylase, inducing terminal differentiation, cell growth arrest and/or apoptosis in neoplastic cells, and /or inducing differentiation, cell growth arrest and/or apoptosis of tumor cells in a tumor.

~~Examples~~Non-limiting examples of such HDAC inhibitors ~~include, but are not limited to:~~are set forth below. It is understood that the present invention includes any salts, crystal structures, amorphous structures, hydrates, derivatives, metabolites, stereoisomers, structural isomers and prodrugs of the HDAC inhibitors described herein. --

Please replace the section beginning at page 20, line 11 and ending on page 44, line 14, with the following rewritten section:

-- A. **Hydroxamic Acid Derivatives** such as suberoylanilide hydroxamic acid (SAHA) (Richon *et al.*, Proc. Natl. Acad. Sci. USA 95,3003-3007 (1998)); m-carboxycinnamic acid bishydroxamide (CBHA) (Richon *et al.*, supra); pyroxamide; trichostatin analogues such as trichostatin A (TSA) and trichostatin C (Koghe *et al.* 1998. Biochem. Pharmacol. 56: 1359-1364); ~~salicylihydroxamic~~salicylhydroxamic acid ~~(SBHA)~~ (Andrews *et al.*, International J. Parasitology 30,761-768 (2000)); suberoyl bishydroxamic acid (SBHA) (U.S. Patent No. 5,608,108); azelaic bishydroxamic acid (ABHA) (Andrews *et al.*, supra); azelaic-1-hydroxamate-9-anilide (AAHA) (Qiu *et al.*,

Mol. Biol. Cell 11, 2069-2083 (2000)); 6-(3-chlorophenylureido) carpoic hydroxamic acid (3Cl-UCHA); oxamflatin [(2E)-5-[3-[(phenylsufonyl) aminol phenyl]-pent-2-en-4-ynohydroxamic acid] (Kim *et al.* Oncogene, 18: 2461 2470 (1999)); A-161906, Scriptaid (Su *et al.* 2000 Cancer Research, 60: 3137-3142); PXD-101 (Prolifix); LAQ-824; CHAP; MW2796 (Andrews *et al.*, supra); MW2996 (Andrews *et al.*, supra); or any of the hydroxamic acids disclosed in U.S. Patent Numbers 5,369,108, 5,932,616, 5,700,811, 6,087,367 and 6,511, 990.

B. **Cyclic Tetrapeptides** such as trapoxin A (TPX)-cyclic tetrapeptide (cyclo-(L-phenylalanyl-L-phenylalanyl-D-pipecolinyl-L-2-amino-8-oxo-9,10-epoxy decanoyl)) (Kijima *et al.*, J Biol. Chem. 268,22429-22435 (1993)); FR901228 (FK 228, depsipeptide) (Nakajima *et al.*, Ex. Cell Res. 241,126-133 (1998)); FR225497 cyclic tetrapeptide (H. Mori *et al.*, PCT Application WO 00/08048 (17 February 2000)); apicidin cyclic tetrapeptide [cyclo(N-O-methyl-L-tryptophanyl-L -isoleucinyl-D-pipecolinyl-L-2-amino-8-oxodecanoyl)] (Darkin-Rattray *et al.*, Proc. Natl. Acad. Sci. USA 93,1314313147 (1996)); apicidin Ia, apicidin Ib, apicidin Ic, apicidin IIa, and apicidin IIb (P. Dulski *et al.*, PCT Application WO 97/11366); CHAP, HC-toxin cyclic tetrapeptide (Bosch *et al.*, Plant Cell 7, 1941-1950 (1995)); WF27082 cyclic tetrapeptide (PCT Application WO 98/48825); and chlamydocin (Bosch *et al.*, supra).

C. **Short chain fatty acid (SCFA) derivatives** such as: sodium butyrate (Cousens *et al.*, J. Biol. Chem. 254,1716-1723 (1979)); isovalerate (McBain *et al.*, Biochem. Pharm. 53: 1357-1368 (1997)); valerate (McBain *et al.*, supra) ; 4-phenylbutyrate (4-PBA) (Lea and Tulsyan, Anticancer Research, 15,879-873 (1995)); phenylbutyrate (PB) (Wang *et al.*, Cancer Research, 59, 2766-2799 (1999)); propionate (McBain *et al.*, supra); butyramide (Lea and Tulsyan, supra); isobutyramide (Lea and Tulsyan, supra); phenylacetate (Lea and Tulsyan, supra); 3-bromopropionate (Lea and Tulsyan, supra); tributyrin (Guan *et al.*, Cancer Research, 60,749-755 (2000)); valproic acid ~~and~~ valproate and Pivanex™.

D. **Benzamide derivatives** such as CI-994; MS-27-275 [N- (2-aminophenyl)-4- [N-(pyridin-3-yl methoxycarbonyl) aminomethyl] benzamide] (Saito *et al.*, Proc. Natl. Acad. Sci. USA 96, 4592-4597 (1999)); and 3'-amino derivative of MS-27-275 (Saito *et al.*,

supra).

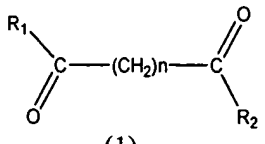
E. **Electrophilic ketone derivatives** such as trifluoromethyl ketones (Frey *et al*, Bioorganic & Med. Chem. Lett. (2002), 12, 3443-3447; U.S. 6,511,990) and α-keto amides such as N-methyl- α-ketoamides

F. **Other HDAC Inhibitors** such as ~~depudecin~~natural products, psammaplins and depudecin (Kwon *et al.* 1998. PNAS 95: 3356-~~3361.~~3361).

Preferred hydroxamic acid based HDAC inhibitors are suberoylanilide hydroxamic acid (SAHA), m-carboxycinnamic acid bishydroxamate (CBHA) and pyroxamide. SAHA has been shown to bind directly in the catalytic pocket of the histone deacetylase enzyme. SAHA induces cell cycle arrest, differentiation and/or apoptosis of transformed cells in culture and inhibits tumor growth in rodents. SAHA is effective at inducing these effects in both solid tumors and hematological cancers. It has been shown that SAHA is effective at inhibiting tumor growth in animals with no toxicity to the animal. The SAHA-induced inhibition of tumor growth is associated with an accumulation of acetylated histones in the tumor. SAHA is effective at inhibiting the development and continued growth of carcinogen-induced (N-methylnitrosourea) mammary tumors in rats. SAHA was administered to the rats in their diet over the 130 days of the study. Thus, SAHA is a nontoxic, orally active antitumor agent whose mechanism of action involves the inhibition of histone deacetylase activity.

Preferred HDAC inhibitors are those disclosed in U.S. Patent Numbers 5,369,108, 5,932,616, 5,700,811, 6,087,367 and 6,511, 990, issued to some of the present inventors disclose compounds, the entire contents of which are incorporated herein by reference, non-limiting examples of which are set forth below:

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 1, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~:

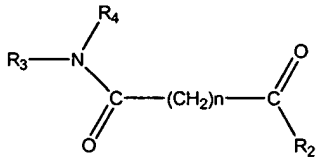


(1)

wherein R_1 and R_2 can be the same or different; when R_1 and R_2 are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine or thiazoleamino group; when R_1 and R_2 are different R_1=R_3-N-R_4, wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl alkyloxy, aryloxy, arylalkyloxy or pyridine group, or R_3 and R_4 are bonded together to form a piperidine group, R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group and n is an integer from about 4 to about 8.

In a particular embodiment of formula 1, R_1 and R_2 are the same and are a substituted or unsubstituted thiazoleamino group; and n is an integer from about 4 to about 8.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 2, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(2)

wherein each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, arylalkyloxy, aryloxy, arylalkyloxy or pyridine group, or R_3 and R_4 are bonded together to form a piperidine group, R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group and n is an integer from about 4 to about 8.

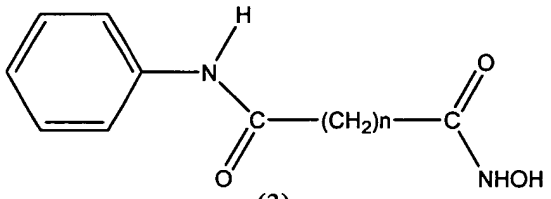
In a particular embodiment of formula 2, each of R_3 and R_4 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group; R_2 is a hydroxylamino, hydroxyl, amino, alkylamino, or alkyloxy group; n is an integer from 5 to 7; and R_3-N-R_4 and R_2 are different.

In another particular embodiment of formula 2, n is 6. In yet another embodiment of formula 2, R_4 is a hydrogen atom, R_3 is a substituted or unsubstituted phenyl and n is 6. In yet another embodiment of formula 2, R_4 is a hydrogen atom, R_3 is a

substituted phenyl and n is 6, wherein the phenyl substituent is selected from the group consisting of a methyl, cyano, nitro, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylamino carbonyl, or hydroxylaminocarbonyl group.

In another embodiment of formula 2, n is 6, R_4 is a hydrogen atom and R_3 is a cyclohexyl group. In another embodiment of formula 2, n is 6, R_4 is a hydrogen atom and R_3 is a methoxy group. In another embodiment of formula 2, n is 6 and R_3 and R_4 bond together to form a piperidine group. In another embodiment of formula 2, n is 6, R_4 is a hydrogen atom and R_3 is a benzyloxy group. In another embodiment of formula 2, R_4 is a hydrogen atom and R_3 is a γ-pyridine group. In another embodiment of formula 2, R_4 is a hydrogen atom and R_3 is a β-pyridine group. In another embodiment of formula 2, R_4 is a hydrogen atom and R_3 is an α-pyridine group. In another embodiment of formula 2, n is 6, and R_3 and R_4 are both methyl groups. In another embodiment of formula 2, n is 6, R_4 is a methyl group and R_3 is a phenyl group.

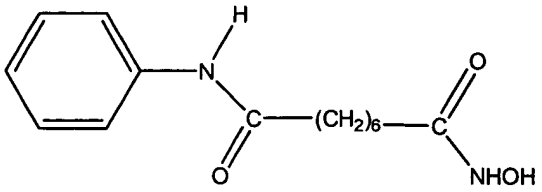
In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 3, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(3)

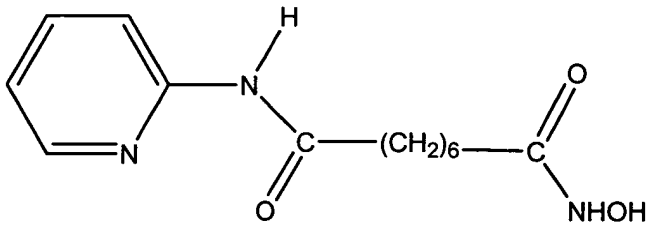
wherein n is an integer from 5 to about 8.

In a preferred embodiment of formula 3, n is 6. In accordance with this embodiment, the HDAC inhibitor is SAHA (4), or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient~~. SAHA can be represented by the following structural formula:



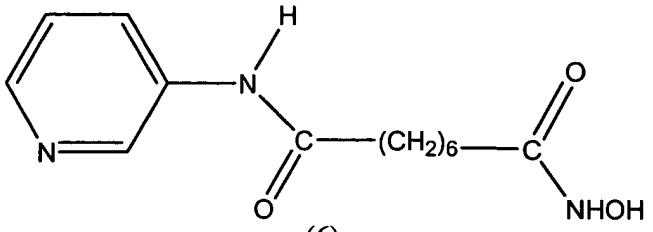
(4)

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 5, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



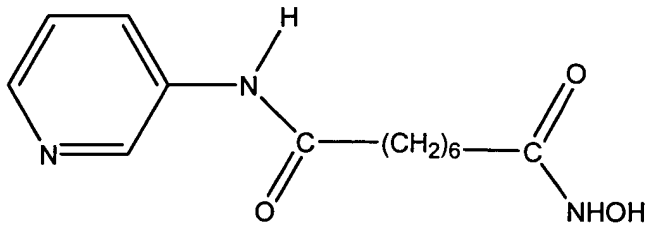
(5)

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 6 (pyroxamide), or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~



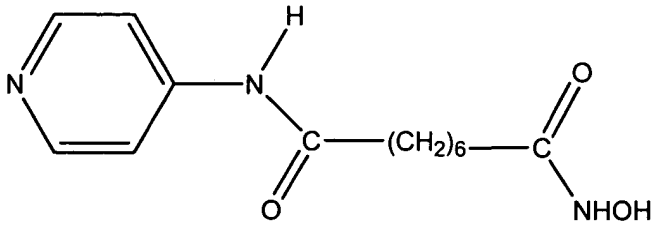
(6)

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 7, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~



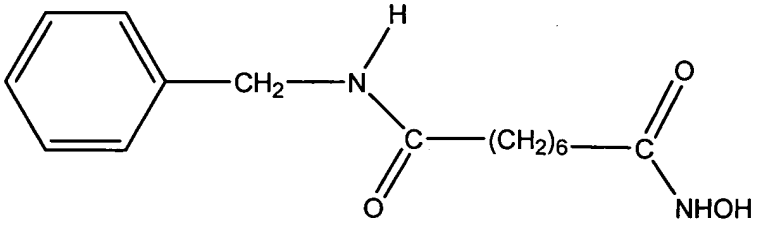
(7)

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 8, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~



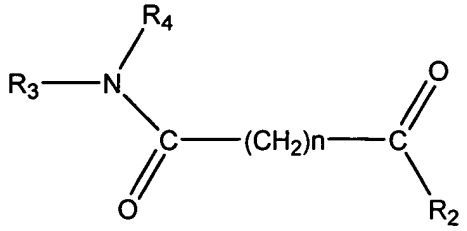
(8)

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 9, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~



(9)

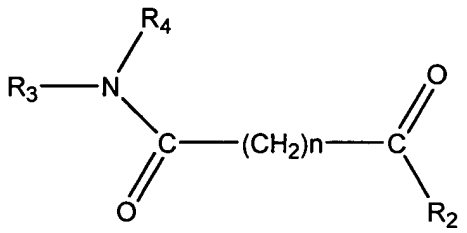
In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 10, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~



(10)

wherein R_3 is hydrogen and R_4 cycloalkyl, aryl, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group; R_2 is a hydroxylamino group; and n is an integer from 5 to about 8.

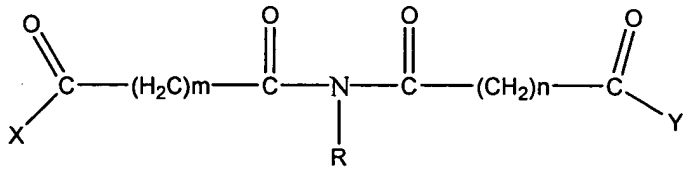
In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 11, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(11)

wherein R_3 and R_4 are independently a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, cycloalkyl, aryl, aryloxy, arylalkyloxy, or pyridine group, or R_3 and R_4 bond together to form a piperidine group; R_2 is a hydroxylamino group; and n is an integer from 5 to about 8.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 12, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



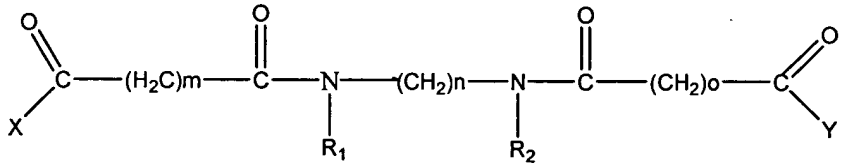
(12)

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or

unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; R is a hydrogen atom, a hydroxyl, group, a substituted or unsubstituted alkyl, arylalkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In a particular embodiment, the HDAC inhibitor is a compound of formula 12 wherein X, Y and R are each hydroxyl and both m and n are 5.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 13, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;

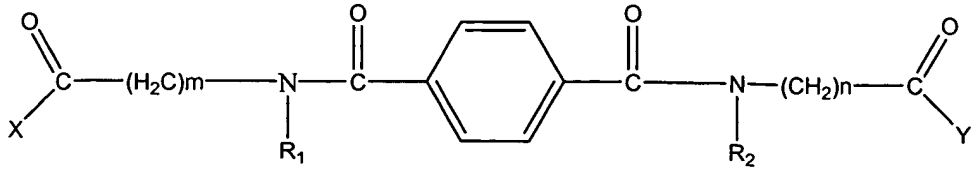


(13)

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m, n and o are independently the same as or different from each other and are each an integer from about 0 to about 8.

In one particular embodiment of formula 13, each of X and Y is a hydroxyl group and each of R_1 and R_2 is a methyl group. In another particular embodiment of formula 13, each of X and Y is a hydroxyl group, each of R_1 and R_2 is a methyl group, each of n and o is 6, and m is 2.

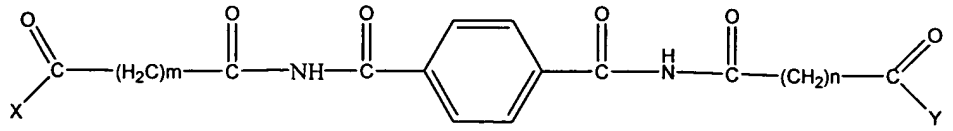
In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 14, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(14)

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 15, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;

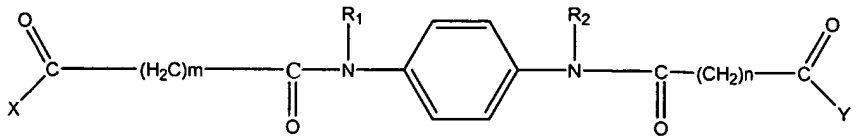


(15)

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In one particular embodiment of formula 15, each of X and Y is a hydroxyl group and each of m and n is 5.

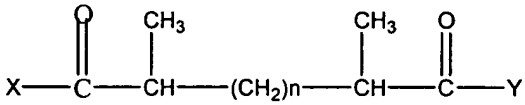
In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 16, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(16)

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, arylalkyloxy or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 17, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;

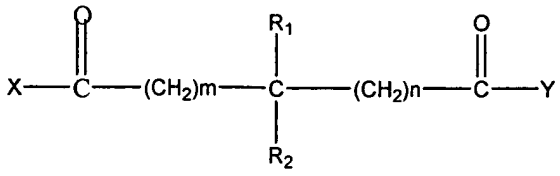


(17)

wherein each of X an Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, or aryloxyalkylamino group; and n is an integer from about 0 to about 8.

In one particular embodiment of formula 17, each of X and Y is a hydroxylamino group; R_1 is a methyl group, R_2 is a hydrogen atom; and each of m and n is 2. In another particular embodiment of formula 17, each of X and Y is a hydroxylamino group; R_1 is a carbonylhydroxylamino group, R_2 is a hydrogen atom; and each of m and n is 5. In another particular embodiment of formula 17, each of X and Y is a hydroxylamino group; each of R_1 and R_2 is a fluoro group; and each of m and n is 2.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 18, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;

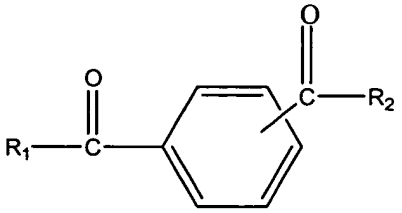


(18)

wherein each of X and Y are independently the same as or different from each other and

are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkyamino or aryloxyalkylamino group; each of R_1 and R_2 are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, aryloxy, carbonylhydroxylamino or fluoro group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

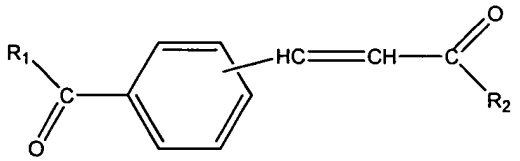
In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 19, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(19)

wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group. In a particular embodiment, the HDAC inhibitor is a compound of structural formula 19 wherein R_1 and R_2 are both hydroxylamino.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 20, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;

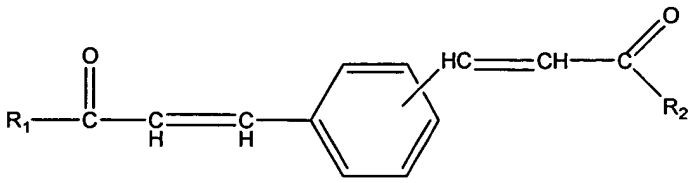


(20)

wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group. In a particular embodiment, the HDAC inhibitor is a

compound of structural formula 20 wherein R_1 and R_2 are both hydroxylamino.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 21, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;

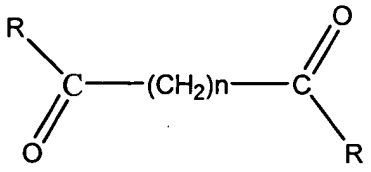


(21)

wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

In a particular embodiment, the HDAC inhibitor is a compound of structural formula 21 wherein R_1 and R_2 are both hydroxylamino

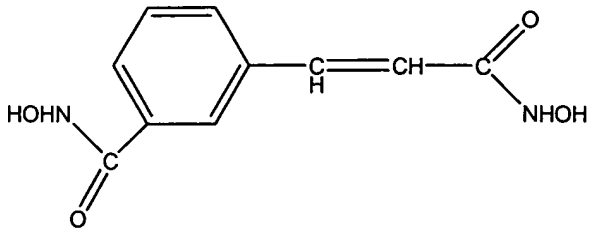
In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 22, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(22)

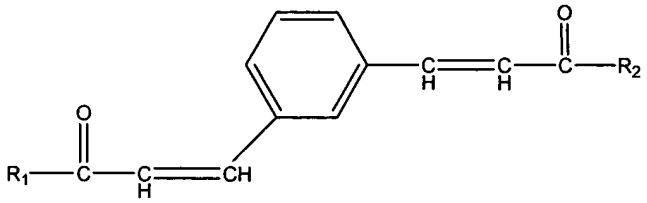
wherein R is a phenylamino group substituted with a cyano, methylcyano, nitro, carboxyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, trifluoromethyl, hydroxylaminocarbonyl, N-hydroxylaminocarbonyl, methoxycarbonyl, chloro, fluoro, methyl, methoxy, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 2,6-difuloro, 3,5-difluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 1,2,3-trifluoro, 3,4,5-trifluoro, 2,3,4,5-tetrafluoro, or 2,3,4,5,6-pentafluoro group; and n is an integer from 4 to 8.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 23 (m-carboxycinnamic acid bishydroxamide - CBHA), or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



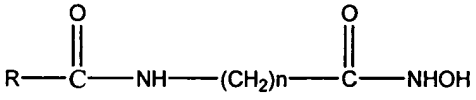
(23)

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 24, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(24)

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 25, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



(25)

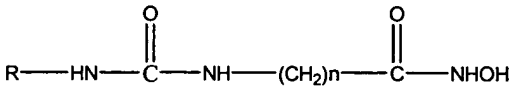
wherein R is a substituted or unsubstituted phenyl, piperidine, thiazole, 2-pyridine, 3- pyridine or 4-pyridine and n is an integer from about 4 to about 8.

In one particular embodiment of formula 25, R is a substituted phenyl group. In another particular embodiment of formula 25, R is a substituted phenyl group, where the substituent is selected from the group consisting of methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methyloxy, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, methyloxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or

hydroxylaminocarbonyl group.

In another particular embodiment of formula 25, R is a substituted or unsubstituted 2-pyridine, 3-pyridine or 4-pyridine and n is an integer from about 4 to about 8.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 26, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



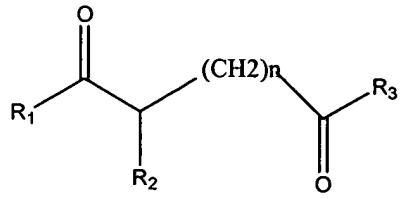
(26)

wherein R is a substituted or unsubstituted phenyl, pyridine, piperidine or thiazole group and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

In a particular embodiment of formula 26, R is a substituted phenyl group. In another particular embodiment of formula 26, R is a substituted phenyl group, where the substituent is selected from the group consisting of methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methyloxy, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, methyloxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

In another particular embodiment of formula 26, R is phenyl and n is 5. In another embodiment, n is 5 and R is 3-chlorophenyl.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 27, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;

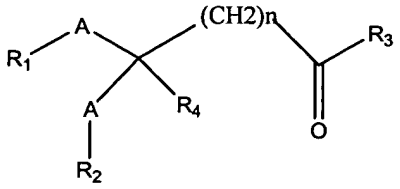


(27)

wherein each of R_1 and R_2 is directly attached or through a linker and is substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, or quinolinyl or isoquinolinyl; n is an integer from about 3 to about 10 and R_3 is a hydroxamic acid, hydroxylamino, hydroxyl, amino, alkylamino or alkyloxy group. The linker can be an amide moiety, e.g., O-, -S-, -NH-, NR_5, $-CH_2-$, $-(CH_2)_m-$, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof, wherein R_5 is a substitute or unsubstituted C_1-C_5 alkyl.

In certain embodiments of formula 27, R_1 is -NH-R_4 wherein R_4 is substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 28, or a pharmaceutically acceptable salt or hydrate thereof~~, and a pharmaceutically acceptable carrier or excipient.~~;



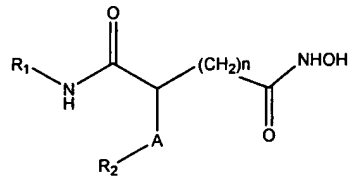
(28)

wherein each of R_1 and R_2 is, substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; R_3 is hydroxamic acid, hydroxylamino, hydroxyl, amino, alkylamino or alkyloxy group; R_4 is hydrogen, halogen, phenyl or a cycloalkyl moiety; and A can be the same or different and represents an amide moiety, O-, -S-, -NH-, NR_5, $-CH_2-$, $-(CH_2)_m-$, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof wherein R_5 is a substitute or unsubstituted C_1-C_5 alkyl; and n and m are each an integer from 3 to 10.

In further particular embodiment compounds having a more specific structure within the scope of compounds 27 or 28 are:

In one embodiment, the HDAC inhibitor useful in the methods of the present

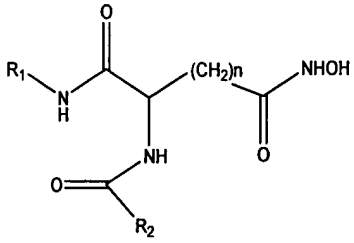
invention is represented by the structure of formula 29, or a pharmaceutically acceptable salt or hydrate thereof:



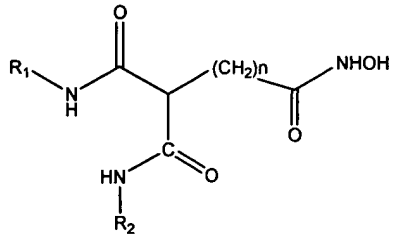
(29)

wherein A is an amide moiety, R_1 and R_2 are each selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; and n is an integer from 3 to 10.

For example, the compound of formula 29 can have the structure 30 or 31:



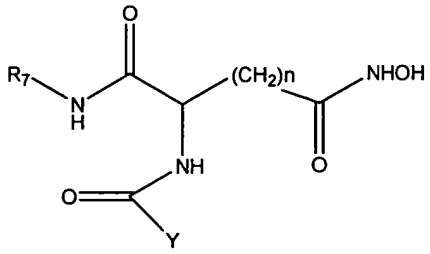
(30)



(31)

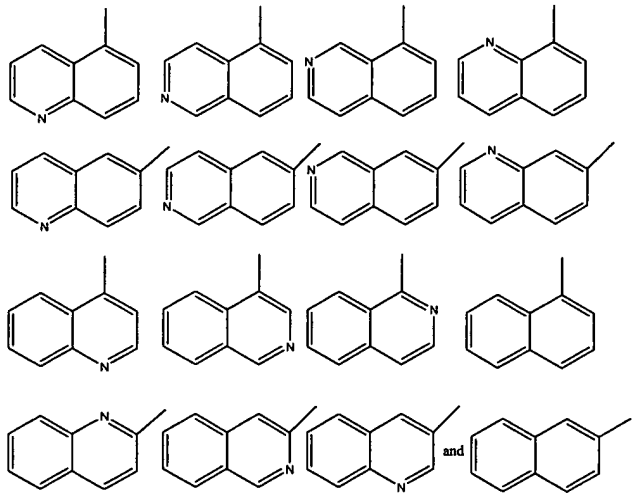
wherein R_1, R_2 and n have the meanings of formula 29.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 32, or a pharmaceutically acceptable salt or hydrate thereof:

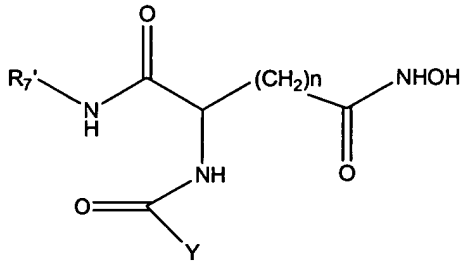


(32)

wherein R_7 is selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; n is an integer from 3 to 10 and Y is selected from:

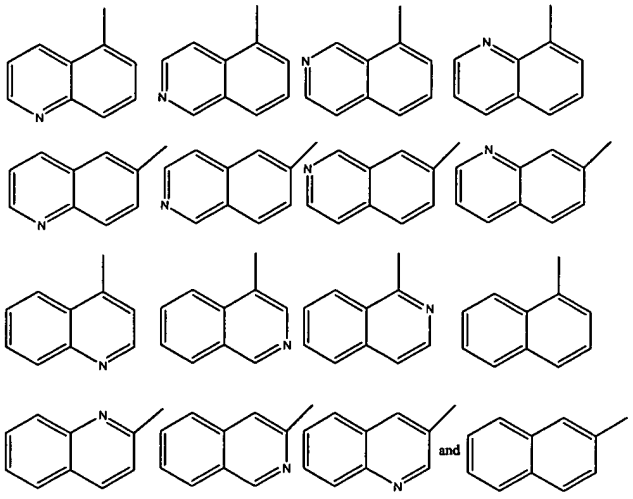


In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 33, or a pharmaceutically acceptable salt or hydrate thereof:

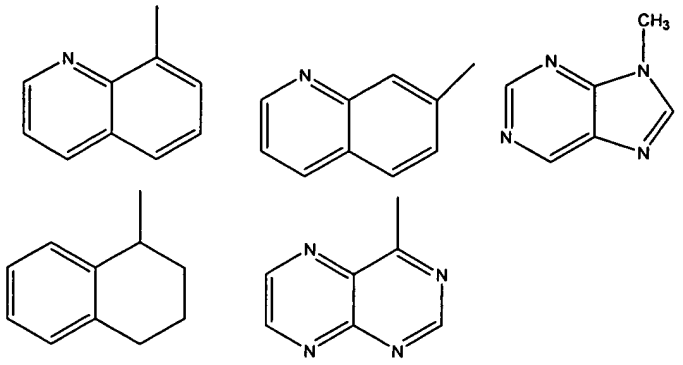


(33)

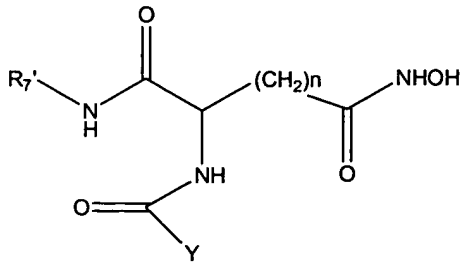
wherein n is an integer from 3 to 10, Y is selected from



and R_7' is selected from

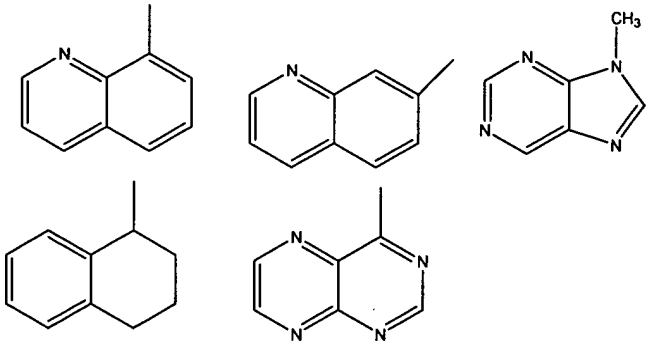


In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 34, or a pharmaceutically acceptable salt or hydrate thereof:

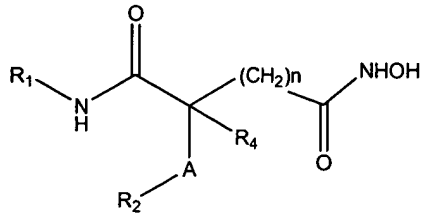


(34)

aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; n is an integer from 3 to 10 and R_7' is selected from



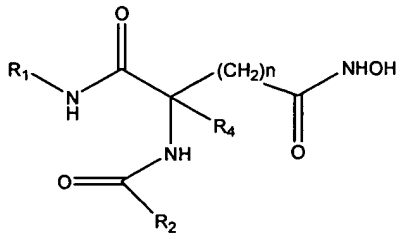
In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 35, or a pharmaceutically acceptable salt or hydrate thereof:



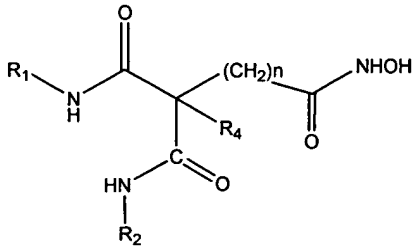
(35)

wherein A is an amide moiety, R_1 and R_2 are each selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; R_4 is hydrogen, a halogen, a phenyl or a cycloalkyl moiety and n is an integer from 3 to 10.

For example, the compound of formula 35 can have the structure 36 or 37:



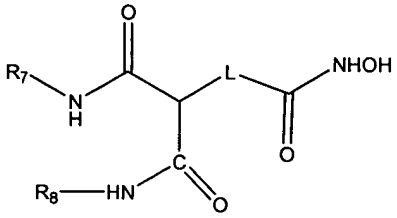
(36)



(37)

wherein R_1, R_2, R_4 and n have the meanings of formula 35.

In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 38, or a pharmaceutically acceptable salt or hydrate thereof:

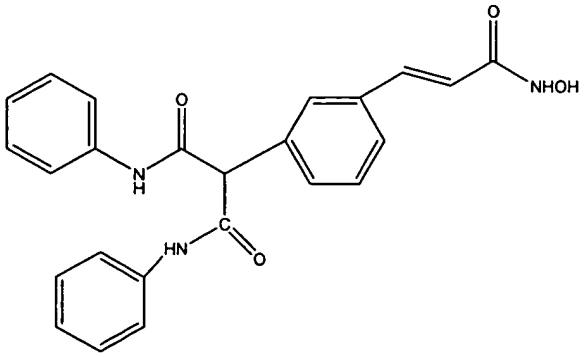


(38)

wherein L is a linker selected from the group consisting of an amide moiety, O-, -S-, -NH-, NR_5, $-CH_2-$, $-(CH_2)_m-$, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof wherein R_5 is a substitute or unsubstituted C_1-C_5 alkyl; and wherein each of R_7 and R_8 are independently a substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; n is an integer from 3 to 10 and m is an

integer from 0-10.

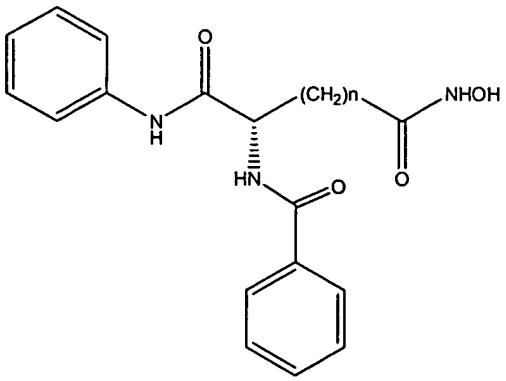
For example, a compound of formula 38 can be represented by the structure of formula (39):



(39)

Other HDAC inhibitors suitable for use in the methods of the present invention include those shown in the following more specific formulas:

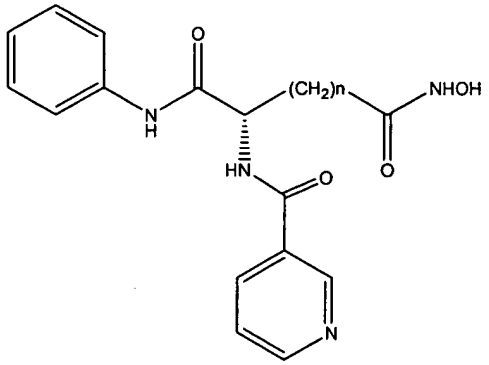
A compound represented by the structure:



(40)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 40, n=5.

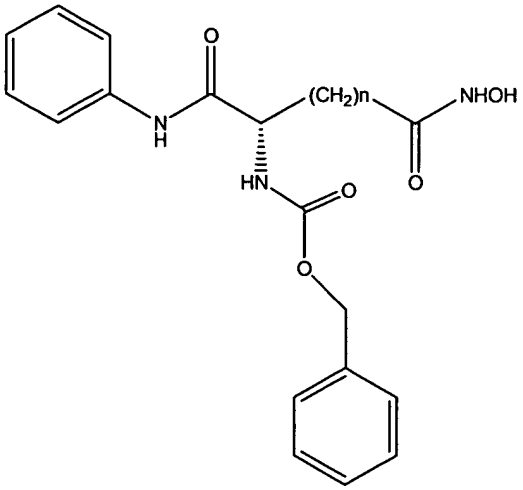
A compound represented by the structure:



(41)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 41, n=5.

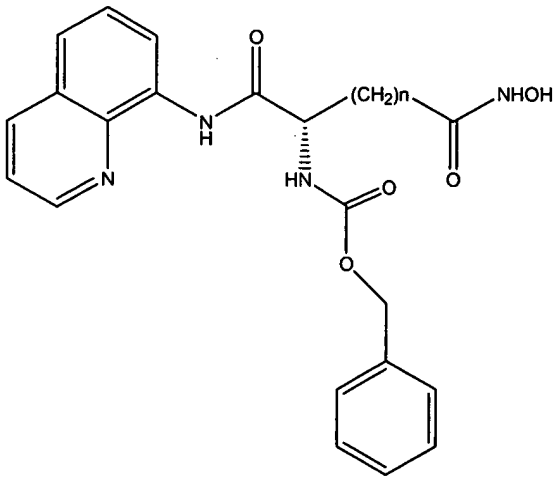
A compound represented by the structure:



(42)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 42, n=5.

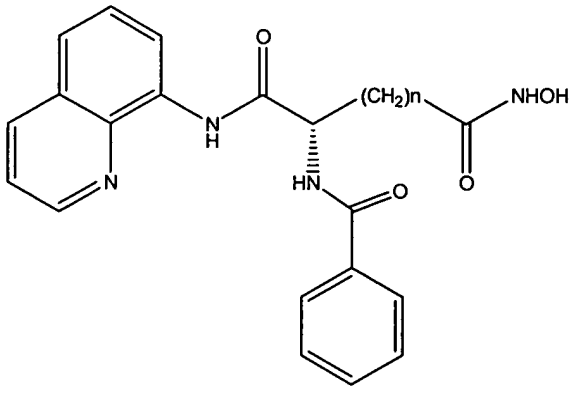
A compound represented by the structure:



(43)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 43, n=5.

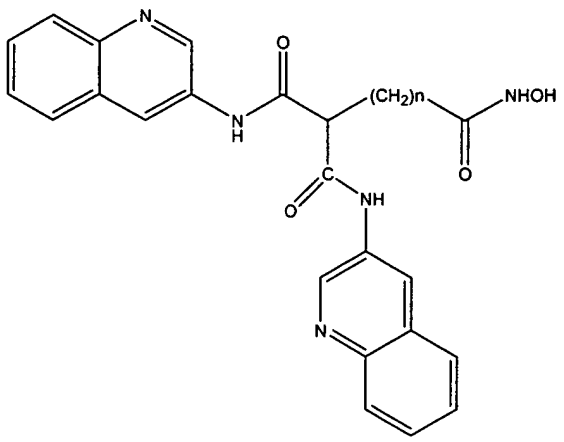
A compound represented by the structure:



(44)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 44, n=5.

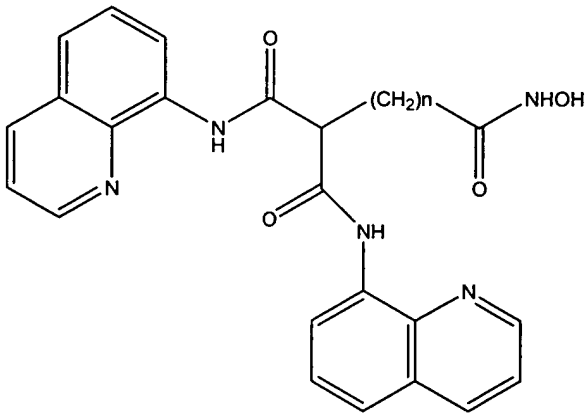
A compound represented by the structure:



(45)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 45, n=5.

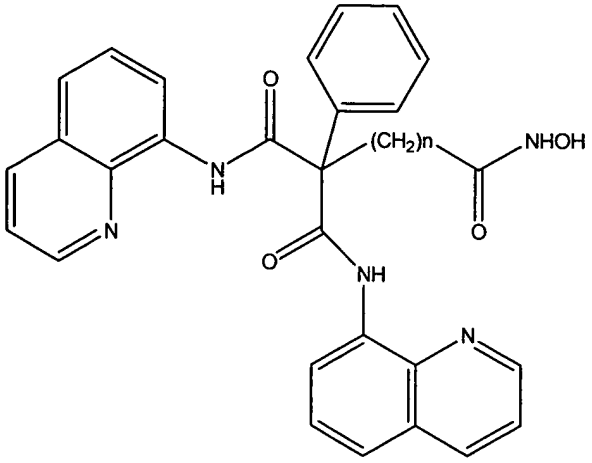
A compound represented by the structure:



(46)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 46, n=5.

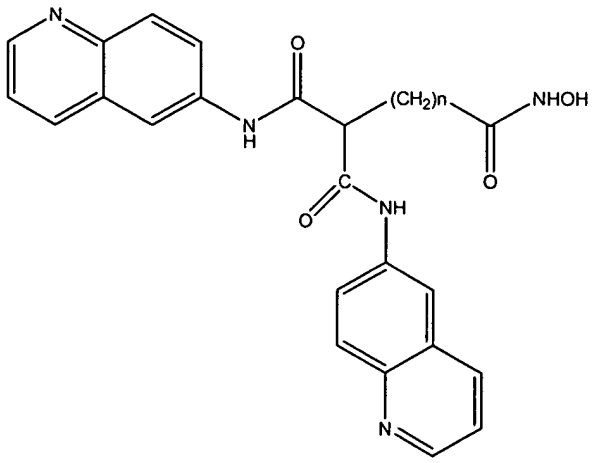
A compound represented by the structure:



(47)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 47, n=5.

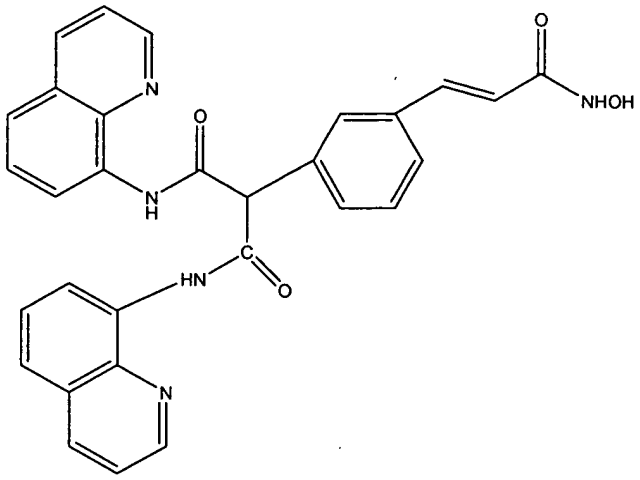
A compound represented by the structure:



(48)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 48, n=5.

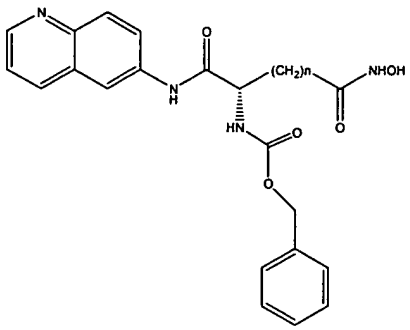
A compound represented by the structure:



(49)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 49, n=5.

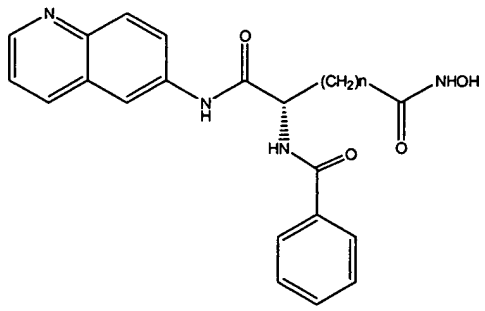
A compound represented by the structure:



(50)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 50, n=5.

A compound represented by the structure:



(51)

wherein n is an integer from 3 to 10 or an enantiomer. In one particular embodiment of formula 51, n=5. --

Please replace the following section beginning at page 46, line 9, ending at page 46, line 17, with the following rewritten section:

-- The invention also encompasses pharmaceutical compositions comprising hydrates of the HDAC inhibitors and/or the anti-cancer agents. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like.

~~This~~In addition, this invention also encompasses pharmaceutical compositions comprising any solid or liquid physical form of SAHA or any of the other HDAC inhibitors. For example, The HDAC inhibitors can be in a crystalline form, in amorphous form, and have any particle size. The HDAC inhibitor particles may be micronized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical form. --